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(71) Applicants: UNIVERSITY OF FLORIDA [US/US]; 223 Grinter Hall, Gainesville, FL 32611 (US). THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 300 Lakeside Drive, Oakland, CA 94612-3550 (US). BACHEM BIOSCIENCE, INC. [US/US]; 3700 Horizon Drive, King of Prussia, PA 19406 (US). BIOMOLECULAR RESEARCH INSTITUTE [AU/AU]; 343 Royal Parade, Parksville, VIC 3052 (AU).

(72) Inventors: KEM, William, R.; 1809 Northwest 47th Street, Gainesville, FL 32605 (US). PENNINGTON, Michael, W.; 32 Delwood Drive, Cherry Hill, NJ 08002 (US). NORTON, Raymond, S.; 353 Royal Parade, Parkville, VIC 3052 (AU). CHANDY, George, K.; 1218 Morningside Drive, Laguna Beach, CA 92651 (US). KALMAN, Katalin; 2017 B Los Trancos, Irvine, CA 92612 (US).

(74) Agent: KITCHELL, Barbara, S.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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*Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

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(54) Title: ShK TOXIN COMPOSITIONS AND METHODS OF USE

(57) Abstract

Disclosed are methods and compositions comprising DNA segments, and proteins derived from sea anemone species. More particularly, it concerns the novel ShK toxin, ShK toxin analogs, chemically-modified toxin analogs, and nucleic acid segments encoding the ShK toxin from *Stichodactyla helianthus*. Various methods for making and using these DNA segments, DNA segments encoding synthetically-modified ShK toxins, and native and synthetic ShK peptides are disclosed, such as, for example, the use of DNA segments as diagnostic probes and templates for protein production, and the use of proteins, fusion protein carriers and peptides in various immunological and diagnostic applications.

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# INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/US 97/22096

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/435 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | M.W. PENNINGTON: "Identification of three separate binding sites on SHK toxin, a potent inhibitor of voltage-dependent potassium channels in human T-lyphocytes and rat brain" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS., vol. 219, February 1996, ORLANDO, FL US, pages 696-701, XP002061813 cited in the application | 1,2,4-9, 15-19, 22,23, 26-36, 39,41-46 |
| Y | see the whole document<br><br>see page 699, paragraph 2 - paragraph 3; table 1 | 3,10-14, 20,21, 24,25, 37,38,40 |
| | --- -/-- | |

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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1

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 9 April 1998 | 20. 05. 1998 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Cervigni, S |

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# INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 97/22096

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X,O | M.W. PENNINGTON ET AL: "Identification of essential residues in the potassium channel inhibitor ShK toxin: analysis of monosubstituted analogs" PEPTIDES: CHEMISTRY, STRUCTURE AND BIOLOGY - PROCEEDINGS OF THE 14TH AMERICAN PEPTIDE SYMPOSIUM, June 1995, ESCOM - LEIDEN, NL, pages 192-194, XP002061814 | 1,2,4-9, 15-19, 22,23, 26-36, 39,41-46 |
| Y | see the whole document<br>see page 194, last paragraph; table 1 | 3,10-14, 20,21, 24,25, 37,38,40 |
| X | J.E. TUDOR ET AL.: "Solution structure of ShK toxin, a novel potassium channel inhibitor from a sea anemone" NATURE STRUCTURAL BIOLOGY, vol. 3, no. 4, April 1996, pages 317-320, XP002061901 | 1-4,7,8, 15-19, 22,23, 26-30, 32, 34-40, 45,46 |
| Y | see the whole document<br>see page 317, column 2, line 4 - line 9 | 3,10-14, 20,21, 24,25, 37,38,40 |
| X | M.W. PENNINGTON ET AL.: "Chemical synthesis and characterisation of ShK toxin" INTERNATIONAL JOURNAL OF PEPTIDE AND PROTEIN RESEARCH, vol. 46, 1995, COPENHAGEN DK, pages 354-358, XP002061815 cited in the application | 1,2,4,7, 8,15-19, 22,23, 26-30, 32, 34-36, 39,45,46 |
| Y | see the whole document | 3,10-14, 20,21, 24,25, 37,38,40 |
| Y | WO 88 06451 A (XOMA CORP) 7 September 1988<br>see the whole document | 3,10-14, 20,21, 24,25, 37,38,40 |
| Y | EP 0 219 716 A (TOA NENRYO KOGYO KK ;TSURU SUMIAKI (JP)) 29 April 1987<br>see the whole document | 3,10-14, 20,21, 24,25, 37,38,40 |

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

In. . ational application No.
PCT/US 97/22096

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/22096

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 1-11, 22-25, 29-40 and at least in part 45-46 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/US 97/22096

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | AU 1421488 A | 26-09-88 |
| | | DE 3875306 A | 19-11-92 |
| | | EP 0303681 A | 22-02-89 |
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